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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,731	12/11/2001	Joseph A. Monforte	24743-2308	5775

20985 7590 06/07/2005

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EXAMINER
COUNTS, GARY W

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,731	MONFORTE, JOSEPH A.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,15,17-23,26-28 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14,15,17-23,26-28 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Status of the claims

The amendment filed March 11, 2005 is acknowledged and has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 17 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutants or variants derived from hemoglobin β gene, does not reasonably provide enablement for any and all mutants or variants derived from any and all genes or for any and all hemoglobin genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of

working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a multiplexed method of detecting a plurality of target polypeptides in a sample, the method comprising: contacting the sample with genetic packages that each display a polypeptide-binding component under conditions whereby the plurality of target polypeptides in the same form complexes with displayed polypeptide-binding components specific therefore, wherein: each genetic package comprises a predetermined marker component that is indicative of its displayed polypeptide-binding component; and the polypeptide-binding component specifically binds to at lest one of the target polypeptides; identifying complexes of the plurality of target polypeptides with the displayed polypeptide-binding components of the genetic packages; detecting the marker components in the genetic packages that have formed complexes, wherein the presence of the maker components indicates the presence of the plurality of target polypeptides; wherein the marker components comprise a plurality of related marker components that are mutants or variants derived from the same gene and wherein the gene is hemoglobin.

The specification on page 41, line 26 – page 42, line 21 discloses the hemoglobin β gene is randomly mutagenized to generate a family of closely related genes that encode hemoglobin proteins of differing masses. The different hemoglobin variants can be distinguished in a variety of detection systems. However, it does not disclose the use of any and all genes or any and all hemoglobin genes and the mutant or variants. Furthermore, the use of such genes and their mutants and variants in genetic packages

is not well known in the art and thus one of ordinary skill in the art would have a low level of predictability in the art. There are no working examples in the specification. At best, the mutants or variants must be derived from hemoglobin β gene. Such is not seen as sufficient to support the breath of the claims and one skilled in the art cannot practice the claimed invention without undue experimentation, because in order to select an appropriate related marker component, one skilled in the art would have to have a high level of predictability, in order to successfully select a related marker component without undue experimentation.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-12, 14, 15, 17-23, 26-28 and 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is unclear how complexed target polypeptides can be detected without a separation or a wash step to remove unbound polypeptides because regardless if the polypeptide-binding component binds the polypeptide of interest, the marker component will be detected. Further, how can one differentiate the bound from unbound? Thus, even when bind occurs and when no binding occurs to the polypeptides the marker component will be detected and a false positive result will always occur. Please clarify.

Claim 2 the recitation "disease related protein" is vague and indefinite. It is unclear what applicant intends. There is no definition provided for the term in the specification and it is unclear what is considered to be a disease related protein.

Claim 17 is vague and indefinite because it is unclear what applicant intends. Does each genetic package comprise marker component and each marker component comprises a mutant or variant that is different from that of the other marker components or does each marker component of the genetic package comprise a plurality of mutants or variants. Please clarify.

Claim 17 "related marker component" is vague and indefinite. The term related is a relative term which renders the claim indefinite. Further, it is unclear how the mutants or variants are related. Are they related by size, color, mass or something else?

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1, 2, 10-12, 18-20, 26, 49 and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Larocca et al (US 6,472,146).

Larocca et al disclose methods for determining protein-protein interactions. Larocca et al disclose that the method can be a multiplexing method (col 11, lines 60-67). Larocca et al disclose contacting a sample such as a cell sample or tissue sample with genetic packages. Larocca et al disclose that the genetic package can be a bacteriophage such as lambda, T4 and M13 (col 4, lines 30-41). Larocca et al disclose that the genetic packages also display a protein or peptide (polypeptide-binding component) on the surface of the genetic package for binding to the protein of the sample. Larocca et al also discloses that the genetic package comprise an expressible nucleic acid molecule for detection (predetermined marker component) (col 4, & col 11). Larocca et al disclose detecting the predetermined marker component to detect the complexes between the genetic packages and the protein or peptides of the sample. Larocca et al disclose amplifying the phages (col. 9). Larocca et al disclose that amplification can be done by PCR.

With respect to detecting target polypeptides as recited in the instant claims. Larocca et al teaches detecting proteins/peptides and according to applicant's definition on page 10, lines 13-16 of the specification "the terms "polypeptide", "peptide," and "protein" are used interchangeably to refer to a polymer of amino acids linked through

peptide bonds. Polypeptides of the include, but are not limited to, proteins". Therefore, Larocca et al teaches the detection of polypeptides.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1- 11, 14, 15, 18-20, 22, 23, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Georgiou (US 5,866,344) in view of Larocca et al (US 6,472,146)

Georgiou discloses immunoassays for the detection and quantitation of analytes using bacterial cells (genetic packages). Georgiou discloses that the methods are particularly useful for the determination of polypeptides (col 6). The bacterial cells (genetic packages) comprise surface-expressed polypeptides which are antibodies. The cell surface-expressed polypeptides may also be antibody conjugates such as fusion proteins that include detection proteins (reporter molecules: beta lactamase,

alkaline phosphatase, luciferase) (predetermined marker component)(col 8). Georgiou disclose that the bacterial cells (genetic packages) may be attached to a solid support (col 7). Georgiou discloses washing steps to remove any unbound material. In practice a set of bacterial cells (genetic packages) comprising surface-expressed polypeptides which are specific for an analyte, are contacted with a sample suspected of containing the analyte. The amount of analyte is detected and resulting fluorescence intensity is quantitatively detected. Georgiou discloses that the invention is readily adaptable to the determination of multiple analytes. Georgiou discloses that this is achieved using two or more different analyte-binding antibodies expressed in separate host cells and using different detecting agents with two different labels (col 8, lines 44-63).

Georgiou differs from the instant invention in failing to specifically state that the method is a multiplex method.

Larocca et al disclose genetic packages used in the detection of analytes. Larocca et al disclose detecting by using multiplexing by using a variety of alternatively colored fluorescent protein expression vectors which can be used as reporter genes to provide multiplexing (col 11). Larocca et al disclose that this provides for a high throughput method of detection.

It would have been obvious to one of ordinary skill in the art to incorporate multiplexing as taught by Larocca et al into the method of Georgiou because Georgiou specifically teaches that method is readily adaptable to the determination of multiple analyte and Larocca et al teaches multiplexing which provides a high throughput

method of detection. Thus one of ordinary skill in the art would have a reasonable expectation of success incorporating multiplexing as taught by Larocca et al into the method of Georgiou.

With respect to the numbers of polypeptides to be detected as recited in the instant claims. The optimal number of ligands to detect the polypeptides can be determined by routine experimentation and thus it would have been obvious to one of ordinary skill in the art to optimize the number of ligands to correspond with the number of polypeptides. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

10. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Georgiou (US 5,866,344) and Larocca et al (US 6,472,146) in view of Hutchens et al (US 2004/0142493).

See above for teachings of Georgiou and Larocca et al.

Georgiou and Larocca et al differ from the instant invention in failing to teach detection by matrix-assisted laser desorption/ionization.

Hutchens et al discloses detecting genetic packages by matrix-assisted laser desorption/ionization (page 5, para. 0049 & page 13, para. 0171). Hutchens et al discloses that this provides for the simultaneous mass screening of very large numbers of genetic packages bearing different polypeptides (page 27, para. 0346).

It would have been obvious to one of ordinary skill in the art to incorporate matrix-assisted laser desorption/ionization mass spectrometry for detection as taught by Hutchens et al into the modified method of Georgiou because Hutchens et al teaches that this provides for the simultaneous mass screening of very large numbers of genetic packages bearing different polypeptides and Georgiou specifically teaches that method is readily adaptable to the determination of multiple analytes. Thus one of ordinary skill in the art would have a reasonable expectation of success incorporating MALDI into the modified method of Georgiou.

Response to Arguments

11. Applicant's arguments filed March 11, 2005 have been fully considered but they are not persuasive.

112 2nd Rejections

Applicant argues that the amendment to claim 1 specifies that complexes of genetic packages with the target polypeptides are identified and the marker component is detected in genetic packages that have formed complexes.and that it is clear from the language of the claim to one of skill in the art that the complexes must be identifiable and, if necessary, separable from the uncomplexed material before detection of the marker component. This is not found persuasive because the claims must stand on their own merits and , it is noted that the features upon which applicant relies (i.e.,

separable from the uncomplexed material before detection of the marker component) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus it is unclear how complexed target polypeptides can be detected without a separation or a wash step to remove unbound polypeptides because regardless if the polypeptide-binding component binds the polypeptide of interest, the marker component will be detected. Further, how can one differentiate the bound from unbound?

Art rejections

12. Applicant's arguments with respect to art rejections have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

13. No claims are allowed.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Wildsmith et al. (US 2002/0142354) disclose arrays for analyzing the protein or peptide content of a sample (abstract). Wildsmith et al disclose immobilizing phage-antibody display systems to the array (example 2) for protein recognition units.

Klempner et al (US 2002/0187464) teaches many different phages each expressing a different binding component for binding to polypeptides in a sample (page 2).

Cardone et al. (US 2002/0076727) disclose labeled phages which displays an antibody fragment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
June 1, 2005

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06/03/05